

Remarks

Claims 1-19, 24 and 25 are currently pending in the application, claims 20-23 are withdrawn from consideration. Claims 1-3, 5, 9-12, 14, 16, 18, 19, 24, and 25 are currently amended; claims 20-23 are withdrawn-currently amended. No new matter has been added. The present amendments result in the exclusion of particular compounds. Given the extensive disclosure of alternatives at all of the positions shown in the disclosed compounds in the specification, combined with the previously presented claim 1 having exclusion of sub-genera, as well as particular species, it is clear that Applicants were in possession of the exclusion of the compounds. Accordingly, Applicants submit that no new matter has been added to the application and that all new claims are fully supported by the specification.

Support for the amended claims claims can be found throughout the specification. Examples of support for the amended claims appear at the following page numbers and paragraph numbers that are referenced with respect to U.S. Patent Application Publication 2005/0215645 A1 of the above-referenced application:

Amended claims 1 and 2

Definition of R⁵, see page 21, paragraph [0230].

Amended claim 3

Definition of Z, see page 21, paragraph [0235];

→ a methylene group was selected.

Amended claim 5

Definition of R¹, the recitation “a group represented by the formula -X-A wherein A represents hydrogen atom or an acyl group, X represents oxygen atom or NH,” was selected from amended claim 1.

Amended claim 10

Four compounds were deleted because these compounds were excluded by the restriction of the scope of amended claim 1.

Amended claim 11

6-Acetylamino-N-benzyl-naphthalene-1-sulfonamide and 6-amino-N-benzyl-naphthalene-1-sulfonamide were deleted because these compounds were excluded by the restriction of the scope of claim 10.

Amended claim 14

Definition of Z, see page 21, paragraph [0235]

→Methylene group was selected.

Amended claim 16

Definition of R¹, the phrase “a group represented by the formula -X-A wherein A represents hydrogen atom or an acyl group, X represents oxygen atom or NH,” was selected from amended claim 2.

Amended claim 18

6-Acetylamino-N-benzyl-naphthalene-1-sulfonamide and 6-amino-N-benzyl-naphthalene-1-sulfonamide were deleted because these compounds were excluded by the restriction of the scope of claim 1.

Amended claims 21, 23 and 24

Definition of R⁵, see page 21, paragraph [0230].

Response To The Office Action**Information Disclosure Statements**

Applicants note with appreciation the Examiner's indication that the Information Disclosure Statements filed on June 20, 2006, April 14, 2005, and January 18, 2005 have been considered. Furthermore, Applicants note that a Third Supplemental Information Disclosure Statement has been submitted concurrently with this response

Priority

The Office Action acknowledges Applicants' claim of priority under 35 U.S.C. §119 and 365 and indicates that a certified copy of the priority document was received by the Office.

Restriction Requirement

Applicants note that the Examiner had previously restricted the claims based upon an alleged lack of unity of invention. With the present amendment, Applicants note that claims 20-23 have been amended, and respectfully submit that these claims share a "special technical feature" as defined in the PCT Unity of Invention rules. In particular, Applicants note that all of the pending claims share the requirement of a substances categorized by the general formula in claim 1.

In the Restriction Requirement dated February 1, 2006, the Examiner relied on compounds categorized as formula (I) of U.S. Patent No. 5,707,985 to McKenzie et al. (McKenzie). With the present amendment, none of the pending claims reads on any compound in McKenzie.

In view of the present amendments and remarks, Applicants respectfully submit that all of the claims satisfy the requirements for unity of invention and that the withdrawn claims should be rejoined. Thus, Applicants respectfully request that the Examiner reconsider and withdraw the Restriction Requirement.

Rejections under 35 U.S.C. § 112

Claims 1-9 and 12-19 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter. The Office Action bases this rejection on an allegedly improper Markush group listing.

In response, Applicants submit that by the above amendment to claims 1 and 12, the claimed compounds are now listed in the alternative. Therefore, Applicants respectfully request withdrawal of this rejection.

Claims 1-10, 12-19, and 24-35 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter. The Office Action asserts this rejection because of a typographical error in claim 1, which inadvertently lists moieties R⁵ twice, instead of reciting moieties R⁵ and R⁶.

Applicants submit that this error has been corrected by the above amendment and respectfully request withdrawal of this rejection.

Claims 1-10, 12-19, and 24-35 are rejected under 35 U.S.C. § 112, first paragraph, because the Office Action alleges that the specification, while being enabling for enhancing the reduction in the survival rate of Jurkat cells when the compounds of the instant invention are administered with bleomycin, does not reasonably provide enablement for treating any cancer.

In response, Applicants traverse this rejection. Applicants emphasize that the present claims are directed towards enhancing the effect of a cancer therapy. Furthermore, the present claims specify that the cancer therapy is based on a mode of action of DNA injury. Antitumor agents such as bleomycin, adriamycin, cisplatin, cyclophosphamide, or mitomycin C are well known to target DNA and have a similar mode of action. These agents target the DNA of cancer tissue and tumors and cause an injury to this target DNA. Examples of such injuries include cleaving of the target DNA and/or crosslinking the complementary strands of the target DNA. As a result, the target DNA is prevented from further proliferation and the cancer tissue and tumors stops in growing followed by degeneration (apoptosis).

The compounds claimed in the present invention enhance the suppressing effect on the proliferation of tumor cells by bleomycin, as well as other antitumor agents. Therefore, someone of ordinary skill in the art would know that the same compounds can be administered with other DNA-targeting antitumor agents, since the suppression of DNA proliferation is desired for the treatment of any cancer.

The Office Action asserts that *the artisan using the invention would be a physician with an MD degree and several years of experience*. Furthermore, the Examiner asserts that *there are certain drugs for certain cancers* and that one skilled in

the art be able to determine which existing drugs are likely to be useful for treating a tumor. However, the Examiner alleges that the application has not fully determined which tumors will and will not respond to the treatment with the instantly claimed compounds.

Applicants respectfully traverse this argument. The artisan, i.e., a physician with several years of experience, is well aware of the mode of action of drugs that are used for treating a certain tumor. That is, the physician would know that an antitumor agent such as bleomycin and any of the other above-mentioned agents target the DNA of cancer tissue and tumors as described above. When informed of the present invention, the physician would also know that administering one of the claimed compounds would support the treatment, i.e., suppression of cancer DNA proliferation benefits the mode of action of the DNA targeting drug.

Furthermore, the aforementioned class of antitumor agents targeting DNA of cancer tissues and tumors are known to have antitumor effect not only on Jurkat cells but on other types of tumor cells. For example, see Jpn. J. Cancer Res., 80, pp.83-88, which was submitted in the Information Disclosure Statement of January 18, 2005. In order to further inform the Office regarding drugs that have anticancer activity on cells other than Jurkat cells, Applicants respectfully submit The Merck Manual of Diagnosis and Therapy, 17th edition, pp. 986-985 in. Therefore, one of ordinary skill in the art would readily understand that the compounds of the present invention can enhance antitumor actions of the above-mentioned class of DNA-targeting antitumor agents on a variety of antitumor cells including Jurkat cells.

In addition, Applicants note that radiation therapy also induces DNA injury, which results in suppression of tumor cells, for example, see Endocrine-Related Cancer, 6, pp. 41-44, 1999. Accordingly, one of ordinary skill in the art would readily understand that the compounds of the present invention can enhance the antitumor efficacy of radiotherapy in view of the present application.

Applicants respectfully submit that the enablement requirement is satisfied. Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections under 35 U.S.C. § 102(b)

The Office Action rejects claims 1-10, 12-17, 24, and 25 under 35 U.S.C. § 102 as being anticipated by at least one of the following references:

- (a) Marsilje et al., Bioorganic & Medicinal Chemistry Letters, 2000, 10, pp. 477-481, compound 2v on page 478;
- (b) Stein et al., J. Med. Chem., 1995, 38, pp. 1344-1354, compound 71 on page 1347; and
- (c) Butenas et al., Biochemistry, 1992, 31, 5399-5411, allegedly disclosing 5-amino-naphtalene-1-sulfonyl-benzamide.

Although the cited documents do not disclose compounds of general formula (I) in claim 1 as medicaments for enhancing an effect in cancer therapy, Applicants note that by the foregoing amendments, the claims have been amended to expressly exclude the

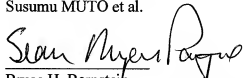
compounds cited by the Office Action. Therefore, Applicants respectfully submit that this rejection is rendered moot and withdrawal of the rejection is respectfully requested.

Conclusion

Reconsideration of the outstanding Office Action and allowance of the present application and all the claims therein are respectfully requested and now believed to be appropriate.

Should the Examiner have any further comments or questions or if any issues remain which can be expeditiously resolved by a telephone conference, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully Submitted,
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Induction of cell death by radiotherapy

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Abstract

Ionising radiation remains one of the most effective tools in the therapy of cancer. It combines the properties of an extremely efficient DNA-damaging agent with a high degree of spatial specificity. Nonetheless, there remain considerable differences in the outcome for treatment of tumours of differing histological type treated by radiotherapy. Tumours arising from lymphoid or germ cells are significantly more radiocurable than most solid tumours of epithelial origin. The molecular mechanisms underlying such differences in cellular radiosensitivity are the subject of current research. When normal mammalian cells are subjected to stress signals - e.g. radiation, chemotherapeutic drugs, oxygen deficiency - a range of gene products involved in the sensing and signalling of such stresses are activated. The response of eukaryotic cells to ionising radiation includes activation of DNA repair pathways and cell cycle checkpoints, with subsequent full 'biological' recovery or cell death. Radiation induces two different modes of cell death termed mitotic or clonogenic cell death, and apoptosis. Until recent years, there was surprisingly little mechanistic understanding of the events following induction of physical damage by radiation and biological outcome for the cell. There have been recent major advances in our understanding of the signal transduction pathways involved in determining the fate of cells after irradiation.

Endocrine-Related Cancer (1999) 6 41-44

Induction and fate of DNA damage by ionising radiation

Photons generated by clinical linear accelerators for therapy induce a range of biochemical lesions in genomic DNA, thought to be the most important subcellular target molecule. The class of lesion whose fate most closely correlates with cell death is the DNA double strand break (dsb), which can be induced by direct ionisation of DNA or indirectly via the generation of free radicals. The majority of lesions are repaired rapidly by highly conserved enzymatic pathways. Mismatched lesions, due to 'structural' repair of breaks without fidelity of the genetic message, lead to mutation, with possible change of cell phenotype. Frank unrepaired breaks may generate chromosomal aberrations. Subsequent cell death may occur after a variable number of cell cycles (Fig. 1). This mode of cell death is exhibited by most non-haematopoietic cell lineages in response to ionising radiation, and is referred to as mitotic or clonogenic cell death. It is considered to be the major mechanism by which the majority of solid tumours respond to clinical radiotherapy.

The correlation between the amount of mitotic cell death, DNA lesion induction and chromosomal aberrations suggests that this pattern of cell death probably

results from failure of cells to completely or accurately repair DNA damage. Recent work in mammalian and yeast model systems suggests that at least two distinct pathways involving some four discrete complexes facilitate the repair of dsbs. In one such pathway, so-called non-homologous recombinational repair, little or no homology of DNA sequence is required for rejoining of breaks. The DNA-dependent protein kinase (DNA-PK) and the RAD50 complex act predominantly during G1/early S phase. By contrast, in homologous recombination extensive homology is required between the region of DNA with a dsb and the repair template. This pathway requires the RAD52 complex, acting mainly at late S/G2, or the breast cancer predisposition genes BRCA1/2 complex, acting in S phase (for review see Hendrickson (1997)).

Apoptosis is an alternative mode of cell death after irradiation, but appears to be preferentially expressed in embryonal and haematopoietic cells, with significantly lower levels of induction in epithelial cell types. Radiation-induced apoptosis was initially considered not to require cell division, and therefore regarded as a form of death expressed in interphase cells. Further investigation revealed that it could be induced readily in the cells of the small intestine, lymphocytes and salivary glands

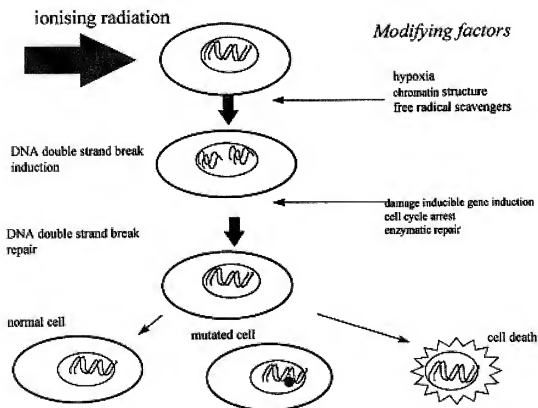


Figure 1 Radiation induced damage to genomic DNA, thought to be the most important subcellular target molecule.

and in experimental tumour systems (Nomura *et al.* 1992, Hendry *et al.* 1995). Given the apparently low levels of radiation-induced apoptosis in the cell types which give rise to most solid human cancers, its relevance to the determination of the response in clinical radiotherapy has been questioned. Studies quantitatively correlating apoptosis events with loss of clonogenic cell survival in non-haematopoietic cells have suggested that the major pathway leading to cell death is mitotic rather than apoptosis. Necessarily many of these data relate to outcomes observed in cell lines. Some mouse tumours treated *in vivo* demonstrate correlations between radiosensitivity and the amount of spontaneous or induced apoptosis.

Clinical regression of solid tumours after completion of therapy is observed over many months, whereas treatment of lymphoid tumours can result in dramatic regression during a course of treatment, perhaps offering circumstantial evidence that cell lineage might be a major determinant of the mode of cell death in response to radiotherapy. This does not preclude a contribution of

spontaneous and induced apoptosis in solid tumours to treatment outcome; however, there is a paucity of clinical data to indicate the true contribution of apoptosis to radiosensitivity (Dewey *et al.* 1995).

Signal transduction of the radiation response and the DNA damage surveillance network

Recently it has been recognised that the cell membrane may be important as a target for at least one pathway of radiation-induced apoptosis (Santana *et al.* 1996). Ionising radiation activates sphingomyelinase, which catalyses the hydrolysis of sphingomyelin to the lipid second messenger, ceramide, thereby inducing interphase death by apoptosis. This pathway has been demonstrated to be deficient in the lymphoblasts of patients with Niemann-Pick disease, a condition in which there is an inherited lack of acid sphingomyelinase. *In vitro*, radiosensitivity can be restored by retroviral transfer of human acid sphingomyelinase cDNA.

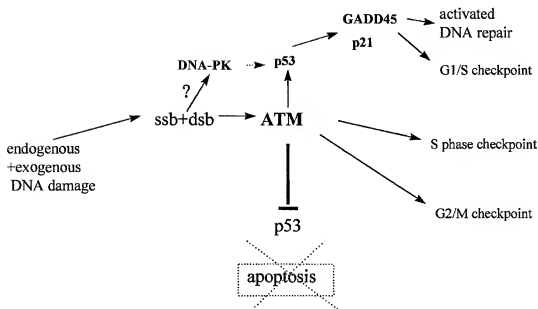


Figure 2 The DNA damage surveillance network.
ssb, single strand DNA breaks

Although the cell membrane is a target for some forms of radiation-induced apoptosis, the nucleus is also a critical target. A major pathway of radiation-induced apoptosis involves DNA damage and subsequent induction of a range of genes including ataxia telangiectasia (AT) and p53 (Fig. 2). In the presence of DNA damage, p53-dependent gene transcription is increased and ubiquitin-dependent degradation of the protein is blocked leading to induction of apoptosis and/or cell cycle arrest. Activation of p53 is mediated via stress-activated protein kinases. In its latent state p53 cannot bind DNA, and it requires phosphorylation to function as a transcription factor. Recent data suggest that DNA-PK is required for the p53 response (Woo *et al.* 1998). DNA-PK modifies the amino-terminal region of p53, which controls its interaction with the transcriptional apparatus and with MDM2. In lymphocytes isolated from p53 knockout mice, clonogenic cell survival is dramatically modulated by inactivation of the p53 response. Expression of a retrovirally transferred mutant p53 transgene in the human ovarian tumour line A2780 produced a significant but lesser increase in radiation resistance, in comparison with the control A2780 cells with an intact p53 response (McIlwrath *et al.* 1994). However, clinical studies examining the relationship between clinical radio-sensitivity and tumour p53 status have largely failed to demonstrate a significant effect.

The AT gene is emerging as another key participant in the cellular response to ionising radiation (Meyn 1995). The phenotype of the rare autosomal recessive disorder ataxia telangiectasia is complex, but key clinical features include progressive cerebellar degeneration, oculocutaneous telangiectasias, immunodeficiency, premature ageing and lymphoreticular malignancies. One per cent of the population is estimated to be heterozygous, with a possible increased risk of solid tumours. Several studies have shown an increased incidence of breast cancer in AT heterozygotes, with a relative risk estimated to be 3.9 (Easton 1994). The AT gene was cloned in 1995, and is 150 kb in length spread over 66 exons. A 13 kb mRNA transcript contains an open reading frame of 9168 bp encoding a 350 kDa nuclear protein (Savitsky *et al.* 1995). Mutations have been detected in over 100 AT patients; over 80% result in truncation of the protein. The similarity of the phenotypes suggests that most of the mutations are functionally equivalent. Sequence comparisons between human mutated in ataxia telangiectasia (ATM) and mouse ATM suggest that the gene is a member of a family of genes involved in cell cycle regulation (TOR1, TOR2, MEC1 of *Saccharomyces cerevisiae* and rad3 of *S. pombe*), telomere length monitoring (TEL1 of *S. cerevisiae*), meiotic recombination (MEC1 of *S. cerevisiae* and mei41 of *Drosophila melanogaster*) and DNA repair (DNA-PK), supporting a key role for ATM in

DNA dsb repair and cell cycle regulation. *In vitro*, cells derived from AT heterozygotes demonstrate increased radiosensitivity in comparison with normal individuals, as measured by chromosomal damage (Chen *et al.* 1994). However, as yet there is no clinical evidence that such individuals have abnormal clinical responses to radiotherapy.

A role for BRCA1 and BRCA2 in the radiation response?

Although analysis of the nucleotide sequence of BRCA1 and BRCA2 failed to yield insight into the likely functions of these genes, recent data have provided compelling evidence for a role in DNA damage response pathways, including the response to ionising radiation (Zhang *et al.* 1998). Both proteins are co-regulated in the cell cycle and associate with human RAD51, the eukaryotic equivalent of the bacterial recombination protein, recA, which is involved in repair of dsbs and chromosome maintenance. The first indirect evidence for a role of BRCA2 in DNA repair was the observation that disruption of BRCA2 in embryos produced ionising radiation hypersensitivity. Direct biochemical evidence for an involvement of the BRCA2 gene product in DNA repair comes from the observation that embryonic fibroblasts isolated from mice bearing a truncating mutation in BRCA2 appear to have altered kinetics in the rejoining of DNA dsb as measured in the single cell gel electrophoresis assay (Connor *et al.* 1997). These mice show a remarkable similarity to Atm-deficient mice, namely, growth retardation (*in vitro* and *in vivo*), absence of mature gametes and shortened lifespan due to the development of thymic lymphoma (Barlow *et al.* 1996). This similarity could indicate a role for both genes in the same DNA damage response pathway, either directly involved in repair, or via low level overexpression of p53 induced by failure of repair. In support of this hypothesis, the growth failure of Atm null fibroblasts is rescued in a p53 null background. We await evidence that the Atm^{-/-} background can rescue the BRCA2 phenotype. Significant questions remain as to the potential relevance of haploid insufficiency in ATM and BRCA2 and implications for cancer predisposition and response to DNA-damaging therapy.

Summary

Knowledge is rapidly increasing of the pathways involved in determining cell fate after exposure to ionising radiation. Many of the genes involved play key roles in genomic stability, and may even participate in determining cancer proneness. Hopefully some of these gene products will provide new targets for therapeutic

modulation of the radiation response and facilitate rational molecular radio-sensitisation.

References

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TABLE 144-2. COMMONLY USED ANTINEOPLASTIC DRUGS (Continued)

Drug class	Drug	Usual Dosage and Route	Mechanism of Action	Cytotoxicity	Commonly Responsive	Toxicity and Remarks
Antibiotics	Doxorubicin (Adriamycin®)	40-75 mg/m ² , IV or SC, every 3-6 weeks by continuous infusion IV or SC	Inhibits uncoupling of strands during DNA replication by forming a complex with topoisomerase II	Non-specific	Acute myeloid leukemia, other lymphomas, breast and lung cancer	Nausea and vomiting, myelosuppression, alopecia, cardiac toxicity as cumulative dose increases; a related derivative, daunorubicin, has been limited to acute leukemia because it has greater cardiac toxicity; less than 1% have died from heart failure after receiving doses up to 900 mg/m ²
Alkylating agents	Bleomycin (Blenoxane®)	6-15 U/m ² /SC or IV	Causes ligation of DNA strands	Non-specific	Squamous cell carcinoma, lymphoma, cancer, lymphoma, leukocytic leukemia	Rash, pulmonary fibrosis as dose increases; edema and fever, skin necrosis, myelosuppression, with neutropenia and thrombocytopenia; 4 to 5 wk therapy rarely causes renal dysfunction > 200 mg/m ² ; requires dialysis
Alkylating agents	Mitomycin	Usually 10 to 12 mg/m ² , slowly IV	Inhibits DNA synthesis by acting as a bifunctional alkylator	Not specific	Gastric adenocarcinoma, colon, rectum, bladder, breast, and lung cancer, transitional cell carcinoma, melanoma	Hemorrhagic cystitis, bone marrow depression, myelosuppression, hemorrhagic cystitis, hemolytic-uremic syndrome
Nitrosoureas	Carmustine (BiCNU®), Lomustine (CeNU®)	150-200 mg/m ² IV 6 wk 100-130 mg/m ² PO q wk	Alkylates DNA with nitrogenous groups and replication of strands	Specific	Brain tumors, lymphoma	Myelosuppression, renal toxicity (Bicnu®), renal toxicity (Lomustine®)
Interferons	Cisplatin (Platino®)	60-100 mg/m ² IV daily x 5 days	Interaction and cross-linking between DNA strands inhibits uncoupling of DNA	Non-specific	Lung cancer (especially small cell), nasopharyngeal cancer, lymphoma	Anemia, ototoxicity, nausea, vomiting, peripheral neuropathy, myelosuppression
Biologic response modifiers	Carboplatin (Paraplatin®), Interferon A (Intron A®)	300 g/m ² or larger area of tumor x 3 days 3-25 x 10 ⁶ U/m ² SC or IV	Same as cisplatin but less nephrotoxic effect	Non-specific	Lung, head and neck, esophageal, gastric cancer, lymphoma	Myelosuppression, fatigue, fever, myalgias, arthralgias, myelosuppression, mild paresthesia (rarely)
Keratins	Azathioprine (Imuran®), Etoposide (Etopos®)	1000-2000 U/m ² IV qd PM 7.5 mg/kg/dose or 80 mg/m ² IV qd	Deposition of epidermal cells at receptor binding sites as well as on cells depend which leukocyte separates on receptors	Cyclic specific	Acute lymphocytic leukemia, small cell cancer, metastatic disease	Keratoconjunctivitis, hyperkeratosis, myelosuppression, hypoglycemia
Hormones	Tamoxifen (Nolvadex®)	10 mg bid	Binding of estrogen receptor	Non-specific	Breast cancer	Hot flashes, hypercalcemia, deep vein thromboses, prothrombotic tendency
	Fulvestrant (Fareston®)	250 mg po q 8 h	Blocks the androgen receptor	Non-specific	Prostate cancer	Hot flashes, decreased libido, irritability at injection site
	Megestrol acetate (Megace®)	160 mg/day	Inhibits testosterone action	Non-specific	Prostate cancer	Decreased libido, hot flashes, gynecomastia
	Testosterone (Andro-Pac®)	100 mg IM weekly	Stimulates androgen production	Specific	Endometrial cancer	Weight gain, fluid retention

given in combination. Sometimes the nausea and vomiting is functional (see Functional Vomiting, Ch. 31) or due to the cancer itself. Therefore, the underlying cause should be identified.

Stimulation of the vomiting center in the medulla can arise in the chemoreceptor trigger zone (CTZ), cerebral cortex, or vestibular apparatus or can be relayed directly from peripheral areas (eg, gastric mucosa). Antiemetics appear to act in these areas, but their mechanism of action is unknown. Generally, drug therapy is more successful for prophylaxis than for treatment of nausea and vomiting.

Serotonin-receptor antagonists are the most effective drugs available for the management of nausea and vomiting associated with radiotherapy or chemotherapy and with anesthesia. These drugs are effective in preventing or reducing the severity of the nausea and vomiting that occurs with granulocyte and ondansetron, although headache and, rarely, orthostatic hypotension have occurred with ondansetron. These drugs are first-line antiemetic therapy; their major drawback is expense.

Phenothiazines (eg, prochlorperazine, fluphenazine), which appear to act by selectively depressing the CTZ and, to a lesser extent, the vomiting center. These second-line drugs are useful in treating mild to moderate nausea and vomiting. Because most phenothiazines (except fluphenazine) are anticholinergics, they may be partially effective if given in sufficient dosage. The choice of drug may depend on consideration of side effects.

Metoclopramide stimulates the motility of the upper GI tract, increases the tone and amplitude of gastric contractions, and increases the rate of gastric emptying. The result is accelerated gastric emptying and intestinal transit.

Metoclopramide functions as an antiemetic by its gastrokinetic effects and, in addition, appears to have some central dopaminergic effects on extracerebral dopamine receptors, which are in part dose-related. Benadryl will protect from these. Other side effects include drowsiness and fatigue. The drug is contraindicated when stimulation of GI motility might be dangerous (mechanical obstruction or perforation) or when the patient has a history of seizures or in patients with, and in epileptics, or in patients

dent, focal pain and tenderness may be clues to an incipient abscess.

A stable patient may be treated with an intravenous or oral regimen; any further deterioration in the patient's condition requires hospitalization is needed. Treatment with broad-spectrum antibiotics should be started immediately after cultures of the blood, sputum, urine, and any suspicious skin lesions are obtained. If diffuse pneumonia is suspected, intravenous therapy should include *Pseudomonas control* (penicillin) in the differential diagnosis and institute empiric therapy, especially in patients with leukemias or lymphomas. In the presence of such infiltrates, the antibiotic regimen should include trimethoprim-sulfamethoxazole, an aminoglycoside, and a cephalosporin. If the patient is febrile, a neutrophilic leukocytosis, gram-positive infections are common and vancomycin should be added. If fever continues after 24 h, a semisynthetic penicillin (eg, ticarcillin) should be added. If fever continues for 72 to 120 h, a fungal infection should be considered. If the patient is unstable, broad-spectrum antibiotics should be added to the therapy program.

An important therapeutic addition during neutropenic sepsis or fever is cytokine therapy with granulocyte colony-stimulating factor (G-CSF) or alternatively granulocyte-macrophage colony-stimulating factor (GM-CSF). G-CSF (5 µg/kg/day sc or by infusion) is the drug of choice and should be instituted at the onset of fever or sepsis.

OTHER COMMON ADVERSE EFFECTS

Enteritis from abdominal radiotherapy can be alleviated with antidiarrheal drugs. Mucositis from radiotherapy can preclude oral intake and may require intravenous fluids and parenteral nutrition. Simple measures (eg, use of analgesics and topical lidocaine be-

fore meals, a bland diet without citrus food or juices, avoidance of temperature extremes) allow the patient to eat and maintain weight. If these simple measures fail, enteral or parenteral nutrition may be required. (Dobhoff) may be considered as long as the small intestine is functionally normal. In cases of mucositis and diarrhea or an abnormally functioning bowel, parenteral alimentation may be substituted. Pain may be a problem in patients with advanced cancer. Radiotherapy or surgery (see Ch. 187) should be considered. In patients with severe, rapidly depression must be recognized. Frank discussion of a patient's fears can often relieve anxiety; a growing amaranthium is now available for treatment of depression (see Ch. 189).

INCURABLE CANCER

A common misconception is that some incurable cancers are benign and that treatment is desirable, that the patient be treated. Treatment means more than the use of surgery, radiotherapy, or chemotherapy; it means the wise care of the patient. For patients whose cancers are not responsive to these modalities, use of an ineffective drug, or the use of a drug that will not cure the cancer is poor medicine. Appropriate therapy for such patients (and for all cancer patients) includes nutritional support, effective pain management, relevant palliative care, and psychiatric and social support. Above all, the patient must know that the specific therapy does not exist or has not been effective. Participation in well-controlled research trials, if available and appropriate, should be considered and discussed with the patient. Hospice or other related end-of-life care programs are important in the management of patients with incurable disease, see Ch. 204.